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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/746,919	12/22/2000	Howard Marcellus Johnson	5600-0001.37	2742

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PERKINS COIE LLP
P.O. BOX 2168
MENLO PARK, CA 94026

EXAMINER
SEHARASEYON, JEGATHEESAN

ART UNIT	PAPER NUMBER
1647	18

DATE MAILED: 06/18/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/746,919	JOHNSON ET AL.	
	Examiner	Art Unit	
	Jegatheesan Seharaseyon	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 March 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *66-71 and 97* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *66-71 and 97* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper N (s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. This office action is response to the amendment filed 3/27/03 in Paper No: 17. Claims 66-71 and 97 are pending.

Specification

2. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. "Ovine interferon tau composition and use thereof to inhibit viral replication" is suggested.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

63a. Claims 66-71 and 97 are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, but whether, if experimentation is necessary, it is undue. See *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404. The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. The factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary

experimentation is "undue" include, but are not limited to: (1) the breadth of the claims; (2) the nature of the invention; (3) the state of the prior art; (4) the level of one of ordinary skill; (5) the level of predictability in the art; (6) the amount of direction provided by the inventor; (7) the existence of working examples; and (8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The specification is insufficient to enable one skilled in the art to practice the claimed invention without an undue amount of experimentation. Applicant has shown data for Peripheral blood mononuclear cells (PBMC) infected with HIV, and HepG2-T14 infected with Hepatitis B, followed by ovine interferon-τ treatment (pages 98-101). The prior art does not disclose that the above-mentioned tissue culture methods are acceptable models for *in vivo* treatment. The therapeutic effect of ovine interferon-τ therapy can be species and model-dependent. In addition, there is no evidence indicating that the disclosed human PBMC or HepG2-T14 cell assay of ovine interferon-τ is an art recognized model to study the anti-viral effect of the ovine interferon-τ (Example 18). *In vitro,* studies often to do not correlate well or predict the *In vivo*, effect of the cytokines. Furthermore, there is no indication that the assay accurately reflects the effect of ovine interferon-τ in the dynamic environment of a living subject.

Although, Applicant described ovine interferon-τ doses to inhibit in cells, there is no guidance provided in choosing the therapeutically effective amount for administering to the subjects to treat the various viral replications (infections) contemplated in the instant inv ntion. There is insufficient evidence of the invention with respect to the *in*

vivo operability of the claimed invention because the specification lacks working examples. Applicant has not disclosed how to use the claimed invention to treat the viral infections caused by the infection of HIV and Hepatitis B virus on the subjects (pages 98-101). The languages of the claims are not strictly limited to *in vitro* treatments and encompass treating patients with viral infections and as such do not have support in the specification. There is insufficient disclosure to reasonably predict that the methods of the instant specification could be used to treat infection by inhibiting replication of the virus *in vivo*. In addition, it is unclear if the same dose indicated will be sufficient for inhibiting both HIV and Hepatitis B viral infection.

Applicant has shown data for Peripheral blood mononuclear cells (PBMC) infected with HIV, and HepG2-T14 infected with Hepatitis B, followed by ovine interferon-τ treatment (pages 98-101), without treating affected subjects or shown an art recognized correlation between the data shown and the scope of the claimed invention. The artisan would recognize and appreciate that there is often no known correlation between *in vitro* and *in vivo* results, because the artisan recognizes that an *in vitro* assay cannot duplicate the complex conditions of *in vivo* treatment. For example, in the *in vitro* assay, the ovine interferon-τ is in contact with cells during the entire exposure period. This is not the case *in vivo* where exposure to the target cells (site) may be delayed or inadequate. In addition, variables such as biological stability, half-life, or clearance from the blood are important parameters in achieving successful therapy. Pharmaceutical therapies are unpredictable for the following reasons; (1) the proteins may be inactivated before producing an effect, i.e. such as proteolytic degradation,

immunological inactivation or due to an inherently short half life protein; (2) the protein may otherwise not reach the target area because, for example, the protein may not be able to cross the mucosa; (3) other functional properties, known or unknown, may make the protein unsuitable for *in vivo use*, i.e. may produce adverse side effects prohibitive to the use of such treatment; (4) the in vivo environment is complex, and not limited to the single cell type used in the assay.

Since applicant has not provided any working examples of the efficacy of using ovine interferon-τ in treating already established disease subjects viral infection, it would require an undue amount of experimentation to one of skill in the art to practice the claimed invention. There are no specific teachings in the disclosure that would allow one to have a reasonable expectation of success in transferring the *in vitro* method to treat viral infections. One is only left with speculation and an invitation to experiment.

Given the breadth of claims 66-71 and 97, in light of the unpredictability of the art as determined by the lack of working examples, the level of skill of the artisan, and the lack of guidance provided in the instant specification and the prior art of record, it would require undue experimentation for one of ordinary skill in the art to make and use the claimed invention of inhibiting all viral infections. In addition, due to the lack of established protocols for effective inhibition viral replication using ovine interferon-τ, undue experimentation would be required to practice the claimed invention and would have little expectation of success.

3b. Claim 67 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while b ing enabling for inhibiting HIV virus r plication does not reasonably provide

enablement for inhibiting Hepatitis C viral replication. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Although, Applicant has shown inhibition of viral replication for HIV (a RNA virus) and Hepatitis B (a DNA virus) using ovine interferon-τ the specification but fails to provide any guidance regarding the inhibition Hepatitis C virus (pages 98-101). There are no working examples to indicate that interferon-τ would indeed inhibit the replication of Hepatitis C infection. In addition, there is no guidance provided in choosing the amount of interferon-τ needed to inhibit Hepatitis C viral replication without increasing the affecting the toxicity in both *in vitro* and *in vivo*. It is also not clear what cells need to be used for testing the efficacy of inhibition. Thus, undue amount of experimentation would be required to establish if ovine interferon-τ would inhibit the viral replication of Hepatitis C.

Applicants have not taught how one of skill in the art would use the full scope of inhibiting both HIV virus and Hepatitis C virus encompassed by the invention of claim 67. The amount of experimentation required to make and/or use the full scope of the claimed method would require trial and error experimentation to determine the cell lines, amount of interferon to be used. Given the breadth of claim 67 in light of the unpredictability of the art as determined by the lack of working examples and shown by the prior at of record, the level of skill of the artisan, and the lack of guidance provided in the instant specification, it would require undue experimentation for one of ordinary skill in the art to use the claimed invention.

4. No claims are allowable.

Contact Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jegatheesan Seharaseyon whose telephone number is 703-305-1112. The examiner can normally be reached on M-F: 8:30-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on 703-308-4623. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-0294 for regular communications and 703-308-4227 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Gary L Kunz

GARY KUNZ
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

JS
June 14, 2003

Remarks

I. Objection to the Specification

The Examiner suggests a new title on the grounds that the title as originally filed is not descriptive.

The Examiner made the same objection in the Office Action dated July 23, 2002. In response, Applicants amended the title to "Antiviral Therapy Using Ovine Interferon Tau" in the response mailed November 25, 2002. Should the Examiner find the title as previously amended not descriptive of the invention, Applicants will again amend the title.

II. Rejections Under 35 U.S.C. § 112, first paragraph

Claims 66-71 and 97 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to make and/or use the invention.

Claim 67 was rejected under 35 U.S.C. § 112, first paragraph, as allegedly non-enabling for inhibiting Hepatitis C viral replication.

Applicants respectfully traverse these rejections.

A. Rejection of Claims 66-71 and 97 as Non-Enabled

In establishing the rejection of claims 66-71 and 97 as non-enabling, the Examiner makes several assertions that are addressed individually.

1. The Examiner's First Assertion

It is the Examiner's position that the claims are not enabled because, while Applicant has shown *in vitro* data for the activity of interferon-τ, the prior art does not disclose that the models on which the data was obtained are acceptable models for *in vivo* treatment (Office Action, page 3, first full paragraph). In short, the Examiner asserts there is no evidence indicating that the cellular assays used are recognized models to study anti-viral effects of ovine interferon-τ (Office Action, page 3, first full paragraph).

In response, Applicants note that:

1. the anti-viral activity of interferon-τ was established and recognized by those of skill in the art as early as 1988;
2. the cellular assays used in Example 18 of the application to support the present claims are the same assays used by those of skill in the art;
3. the anti-viral activity of interferon-τ was evaluated *in vivo* by inoculating 24 newborn lambs with ovine lentivirus and treating a group of the lambs with intererfon-τ, as reported in Applicants' specification on page 35, lines 11-30; and
4. the M.P.E.P is quite clear in stating that "a rigorous or an invariable exact *in vitro*/*in vivo* correlation" is not the standard for compliance with enablement.

Each of these points is addressed in the following paragraphs.

With respect to the first and second points, the anti-viral activity of interferon-τ was reported by Pontzer *et al.* in 1988 in *Biochem. Biophys. Res. Comm.*, 152(2):801 (copy enclosed). A second paper by Pontzer appeared in 1990 in *Proc. Natl. Acad. Sci. USA* (87:5945 (1990)), also reporting on the anti-viral properties of interferon-τ (copy enclosed)[1]. In both papers, Pontzer *et al.* use the same antiviral assay utilized by the present applicants – inhibition of viral replication in Madin-Darby bovine kidney (MDBK) cells using vesicular stomatitis virus as the challenge virus (see Example 2 on page 63 and Example 10 on page 79 of the specification; see page 802 of Pontzer *et al.*-1988; see page 5946, Col. 1 of Pontzer *et al.*-1990).

Applicants specification additionally provides analysis of antiviral activity of interferon-τ in other cells lines, sheep normal fibroblasts (see Example 10 on page 79), peripheral blood mononuclear cells (Examples 11 and 12, pages 80, 82), and HepG2-T14 cells (a human hepatocyte cell line; Example 18, pages 98-101).

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[1]The present application has a priority date of March 2, 1989. Thus, the 1990 paper by Pontzer *et al.* is not effective prior art. The 1988 paper by Pontzer *et al.* was published in April 1988. Thus, the document is not a §102(b) reference. Nor does the document qualify as prior art under §102(a), since Pontzer is an named inventor and an "applicant's disclosure of his or her own work within the year before the application filing date cannot be used against him or her under 35 U.S.C. 102(a)." M.P.E.P. §2131.01.

Furthermore, and with respect to point 3 above, the anti-viral activity of interferon-τ was evaluated *in vivo* by inoculating 24 newborn lambs with ovine lentivirus and treating the lambs with interferon-τ, as reported in Applicants' specification on page 35, lines 11-30. The lambs treated with interferon-τ had a reduced blood viral titer relative to animals not treated with interferon-τ (page 35, lines18-20).

According to the M.P.E.P. § 2164.02, a rigorous or an invariable exact *in vitrolin vivo* correlation is not required (citing to *Cross v. Iizuka*, 753 F.2d 1040, 1050, 224 USPQ 739, 747 (Fed. Cir. 1985). As stated in *Cross*: "based upon the relevant evidence as a whole, there is a reasonable correlation between the disclosed *in vitro* utility and an *in vivo* activity, and therefore a rigorous correlation is not necessary, where the disclosure of pharmacological activity is reasonably based upon the probative evidence."

In the present claims, a method of inhibiting viral replication by contacting cells infected with a virus with a dose of interferon-τ of at least about $5x10^4$ U/day is recited. The anti-viral activity of interferon-τ is clearly established by the *in vitro* data and by the *in vivo* data. The cellular assays are the same as assays used in the published literature.

In light of the data present in the specification in support of the claims, Applicants respectfully request that the Examiner withdraw the rejection.

2. <u>The Examiner's Second Assertion</u>

The Examiner asserts that "the therapeutic effect of ovine interferon-τ therapy can be species and model-dependent."

Applicants are unaware of any document that supports this assertion. Nor has the Examiner provided a reference to support this argument. If the Examiner is aware of a teaching to support this, Applicants are entitled to a copy for review.

3. <u>The Examiner's Third Assertion</u>

The Examiner also asserts that there is no guidance provided in the specification in choosing the therapeutically effective amount for administering interferon-τ to treat various viral replications (Office action, paragraph bridging pag s 3-4). That is

because there are no *in vivo* working examples, the invention lacks operability, and there is insufficient disclosure to reasonably predict that interferon-τ could be used to treat a viral infection *in vivo* (Office action, paragraph bridging pages 3-4). Moreover, it is unclear to the Examiner if the dose indicated would be sufficient for inhibiting both HIV and Hepatitis B viral infections.

As noted above, *in vivo* data is provided on page 35, lines 11-22 of the specification.

With respect to the Examiner's concern that the dose indicated would be sufficient for inhibiting both HIV and hepatitis B viral infections, Applicants note that the standard for enablement is that the specification describe "how to make and how to use the invention." M.P.E.P. § 2164. The present invention is directed to a method of inhibiting viral replication by contacting cells infected with a virus with a dose of interferon-τ of at least about $5x10^4$ U/day is recited. A person of skill in the art is taught how to make the invention by the teachings in the specification on providing interferon-τ and preparing it for contact with cells. A person of skill in the art is taught how to use the invention by the teachings in the specification on how to contact a cell, *in vitro* or *in vivo*, with a dose of interferon-τ.

Claim 1 specifies a minimum dose of interferon-τ to be provided to the infected cell. The dosage was determined based on the studies described above, as well as the other studies reported in the specification, and on the finding that interferon-τ has a low cytotoxicity. As discussed on page 57, line 32 to page 58, line 10, the low toxicity of the protein permits administration at doses higher than that for other interferons.

In accord with M.P.E.P. § 2164.04, Applicants submit that the specification contains a teaching of the manner and process of making and using the invention in terms that correspond to in scope to the claims. This teaching must be taken as being in compliance with the enablement requirement of 35 U.S.C. § 112, first paragraph unless there is a reason to doubt the objective truth of the statements. The Examiner has given no reason to doubt the truth of the teachings in the specification.

4. The Examiner's Fourth Assertion

The Examiner further asserts that "there is often no known correlation between *in vitro* and *in vivo* results, because the artisan recognizes that an *in vitro* assay cannot duplicate the complex conditions of *in vivo* treatment." (Office Action, page 4, first full paragraph). The Examiner continues, stating that "pharmaceutical therapies are unpredictable" and lists four reasons for the unpredictability. Thus, according to the Examiner, since Applicant has not provided any working examples of the efficacy using ovine interferon-τ in treating already established disease subjects viral infection (sic), it would require undue experimentation to practice the claimed invention, and that there is no reasonable expectation of success in transferring the *in vitro* method to treat viral infections. (Office Action, page 5, first full paragraph).

As discussed above, Applicants specification provides analysis of antiviral activity of interferon-τ in Madin-Darby bovine kidney (MDBK) cells using vesicular stomatitis virus as the challenge virus (see Example 2 on page 63 and Example 10 on page 79 of the specification), in sheep normal fibroblasts cells using vesicular stomatitis virus as the challenge virus (see Example 10 on page 79), in peripheral blood mononuclear cells infected with feline immunodeficiency retrovirus (Examples 11 and 12, pages 80, 82), and HepG2-T14 cells infected with hepatitis B (Example 18, pages 98-101). The anti-viral activity of interferon-τ was evaluated *in vivo* by inoculating 24 newborn lambs with ovine lentivirus and treating the lambs with interferon-τ (page 35, lines 11-30).

In light of the ample data provided in the specification, the Examiner's assertion cannot stand, and withdrawal of the rejection of the claims is respectfully requested.

B. Rejection of Claim 67 as Non-Enabled

The Examiner asserts that while the specification is enabling for inhibiting HIV virus replication, it does not reasonably provide enablement for inhibiting hepatitis C viral replication. The lack of working examples for inhibition of hepatitis C virus translates into undue experimentation to make and use the claimed method – since no guidance as to cell lines or amount of interferon for inhibition of hepatitis C viral replication is given. (Office Action, page 6, first and second full paragraphs).

The specification is replete with examples of suitable cell lines and assay for testing the anti-viral activity of interferon-τ (see the summary of *in vitro* data above in A.4.). In light of these examples, it is hard to imagine that a person of skill in the art would be unable to select a cell line, infect the cells with hepatitis C virus, and contact the cells with a dose of interferon-τ in the dose set forth in the claim or at a dose selected based on the guidance in the specification. If the Examiner can establish that one of skill in the art would be unable to conduct what is a routine test for those involved in *in vitro* testing of therapeutic agents, the Applicants would like to review any evidentiary support.

Accordingly, withdrawal of the rejection of claim 67 under 35 U.S.C. § 112, first paragraph is respectfully requested.

III. Conclusion

Applicants submit that the claims are now in condition for allowance, and a Notice of Allowance is respectfully requested. The Examiner is invited to call the undersigned at (650) 838-4402 as needed.

Respectfully submitted,

Judy M. Mohr

Date: 9/17/03

Judy M. Mohr
Registration No. 38,563

Correspondence Address
Customer No. 22918
(650) 838-4300